SUPPORT FOR THE AMENDMENTS

Applicants have amended Claim 1 to change "comprises" to "consists of" and to change "an active ingredient selected from the group consisting of salmeterol, a stereoisomer thereof, and a physiologically acceptable salt thereof" to "salmeterol, a stereoisomer thereof, or a physiologically acceptable salt thereof". Support for amended Claim 1 can be found in the same claim, as previously presented. Claims 2, 3, 8, 9, 12, 13, and 16 have been amended to properly depend from Claim 1. Accordingly, support for amended Claims 2, 3, 8, 9, 12, 13, and 16 can be found in the same claims, as previously presented. Claim 17 has been amended for clarity. Support for amended Claim 17 can be found in the same claim, as previously presented.

No new matter has been added. Claims 1-9 and 12-14, and 16-22 are pending in this application.

REMARKS/ARGUMENTS

Present Claims 1-9 and 12-14 relate to pharmaceutical aerosol formulations to be administered by a pressurized metered dose inhaler, which consist of:

salmeterol, a stereoisomer thereof, or a physiologically acceptable salt thereof, in solution in a propellant system, said propellant system comprising a liquefied HFA propellant, a co-solvent and 0 to 5% w/w water,

wherein said cosolvent is present in an amount which is no more than 35% w/w based on the total weight of said formulation, and

wherein said formulation has a pH of 2.5 to 5.5, and

wherein said pH of said formulation has been adjusted by addition of a mineral acid.

Claims 16 and 17 relate to methods of preparing such a pharmaceutical formulation, and Claims 18-22 relate to methods for the treatment of certain respiratory diseases by administering such a formulation.

The rejection of Claims 1-7, 12, 13, and 15 under 35 U.S.C. § 103(a) in view of U.S. Patent No. 6,423,298 (McNamara et al.); the rejection of Claims 8, 9, and 14 under 35 U.S.C. § 103(a) in view of McNamara et al. and further in view of WO 00/06121 (Keller et al.) wherein U.S. Patent No. 6,585,958 is used as an English language equivalent; and the rejection of Claims 8, 9, 14, 16, and 17 under 35 U.S.C. § 103(a) in view of McNamara et al. in further view of U.S. Patent No. 6,455,028 (Wulffhart et al.) are respectfully traversed.

As explained in the specification, one technical problem to be solved by the present invention may be regarded as providing an improved pharmaceutical formulation of salmeterol, in particular wherein the formulation is able to deliver a significant fraction of particles having a diameter equal to or less than 1.1 μm. This technical problem is solved by providing a formulation of salmeterol in a HFA propellant, a co-solvent and water and wherein the formulation has a pH of 2.5 to 5.5, adjusted by the addition of a mineral acid.

McNamara et al. relates to:

> stable aerosol formulations with fluorohydrocarbons as propellants, particularly TG 134a and/or TG 227, consisting of two or more active substances, wherein at least one active substance is formulated as a solution and ***at least one active substance is formulated as a suspension***.

See, col. 2, lines 21-26, emphasis added.

In McNamara et al., salmeterol is only generically cited and it is described neither alone nor in combination with any active ingredient in any one of the examples. Moreover McNamara et al. relates to formulations in whic ***at least one active substance is formulated as a suspension***. In sharp contrast, the present claims are related to compositions which contain salmeterol in ***solution*** in the propellant-cosolvent system.

In this regard, it is emphasized that the technical fields of aerosol solution and suspension formulations are well separated one from the other, each one posing distinct and specific problems.

In a propellant driven solution composition, the active material is fully dissolved in the propellant/cosolvent system and a suitable amount of cosolvent having a higher polarity than the propellant has to be added in order to solubilize the active ingredient in the propellant.

In contrast, in a suspension composition, the active ingredient must be insoluble in the propellant: even partial solubility of the active ingredient has to be avoided in that it may cause crystal growth, solvate formation, polymorph interconversion, thereby impairing the spray characteristics of the composition.

Moreover, in a suspension formulation, the low volatility component is usually a surfactant or a dispersing aid to obtain the desired physical stability of the suspension by preventing aggregation of the primary drug particles, with the predominant stabilising mechanism being steric repulsion between the projecting hydrophobic chains.

Furthermore, McNamara et al. does not disclose or suggest "that a proper amount of water can favourably affect the solubility of the active ingredient in the HFA:cosolvent mixtures so allowing to reduce the amount of the cosolvent" (*see*, page 8, lines 24-26, of present specification).

In summary, the subject matter of present Claim 1 differs from the formulations of McNamara et al. at least because: (1) of the presence of salmeterol not in combination with any other active ingredient; (2) it is a solution and it does not comprise at least one active substance in the form of suspended particles in the liquid phase; and (3) it comprises a proper amount of water to affect the solubility of the active ingredient in the HFA:cosolvent mixtures.

Applicants submit that there is nothing in either Keller et al. or Wulffhart et al. which can cure the deficiencies of McNamara et al.

In particular, Keller et al. relates to a propellant mixture for aerosols, comprising dinitrogen monoxide and a hydrofluoroalkane. Salmeterol xinafoate is exemplified in Example 10, in combination with glycopyrronium bromide, forming a ***suspension*** formulation.

Wulffhart et al. relates to aerosol formulations comprising nonacicular particles of ipratropium, a propellant and ***substantially free of*** both surfactant and ***solvent***.

None of the cited references suggest modifying the formulation as in present Claim 1 by dissolving salmeterol in a HFA propellant, a co-solvent and water and wherein the formulation has a pH of 2.5 to 5.5 by addition of a mineral acid to obtain a higher fraction of smaller respirable particles.

In conclusion, the specific characteristics of the formulation of the present claims could not be derived from the teachings of the cited references, neither taken alone nor in combination.

For all of these reasons, the rejections should be withdrawn.

The rejection of Claims 16 and 17 under 35 U.S.C. § 112, second paragraph, has been obviated by amendment. As the Examiner will note, these claims have been amended such that they are free of the criticism outlined on page 3 of the Office Action. Thus, the rejection is no longer tenable and should be withdrawn.

The objection to Claim 17 has also been obviated by amendment. Again, this claim has been amended as suggested on page 3 of the Office Action. Accordingly, the rejection is no longer tenable and should be withdrawn.

The rejection of Claims 1-3, 6, 7, 12-14, and 18-21 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 7-10, 21, and 22 of U.S.

Patent No. 7,347,199 ("the '199 patent") in view of McNamara et al. is respectfully traversed. Specifically, there is nothing in McNamara et al. which can cure the deficiencies of the '199 patent claims or suggest the present claims. As noted above, the formulations of McNamara et al. differ from those of the present claims at least because: (1) of the presence of salmeterol not in combination with any other active ingredient; (2) it is a solution and it does not comprise at least one active substance in the form of suspended particles in the liquid phase; and (3) it comprises a proper amount of water to affect the solubility of the active ingredient in the HFA:cosolvent mixtures.

For all of these reasons, the rejection should be withdrawn.

The provisional rejection of Claims 1-3, 5-7, 9, 12, and 14-17 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 2, 3, 6, 7, 11, 19, 22, 24, 28-32, 35, 36, 40-47, and 50-52 of co-pending U.S. Patent Application Serial No. 10/504,151 ("the '151 application") in view of U.S. Patent No. 6,716,414 (Lewis et al.) is respectfully traversed. Specifically, there is nothing in the combination of Claims 2, 3, 6, 7, 11, 19, 22, 24, 28-32, 35, 36, 40-47, and 50-52 of the '151 application and Lewis et al. which would suggest a formulation which contains salmeterol, a stereoisomer thereof, or a physiologically acceptable salt thereof, and which has a pH of 2.5 to 5.5. Accordingly, the provisional rejection should be withdrawn.

The provisional rejection of Claims 1-3 and 5 under the judicially-created doctrine of obviousness-type double patenting in view of Claims 14, 15, 25, and 26 of co-pending U.S. Patent Application Serial No. 11/408,026 ("the '026 application") in view of McNamara et al. is respectfully traversed. Specifically, there is nothing in McNamara et al. which can cure the deficiencies of the '026 application claims or suggest the present claims. As noted above, the formulations of McNamara et al. differ from those of the present claims at least because: (1) of the presence of salmeterol not in combination with any other active ingredient; (2) it is a

solution and it does not comprise at least one active substance in the form of suspended particles in the liquid phase; and (3) it comprises a proper amount of water to affect the solubility of the active ingredient in the HFA:cosolvent mixtures.

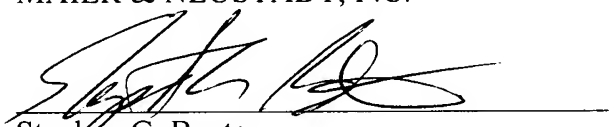
For these reasons, the rejections should be withdrawn.

Lastly, since product Claim 1 is now allowable and since method Claims 18-22 all depend from Claim 1, Claims 18-22 should be rejoined and allowed.

Applicants submit that the present application is now in condition for allowance, and early notification of such action is earnestly solicited.

Respectfully submitted,

OBLON, SPIVAK, McCLELLAND,
MAIER & NEUSTADT, P.C.



Stephen G. Baxter
Attorney of Record
Registration No. 32,884

Customer Number
22850

Tel: (703) 413-3000
Fax: (703) 413 -2220